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(54) **Analgesic process and composition.**

(57) A process for the management of pain comprises the administration of a narcotic analgesic and ibuprofen or flurbiprofen, or a salt or ester thereof. The active ingredients may be combined in a single composition.

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ANALGESIC PROCESS AND COMPOSITION

This invention relates to a process and a composition for the management of pain by the administration of narcotic analgesics.

Narcotic analgesics have been used for the relief 5 of moderate to severe pain. Severe pain, particularly, has required the use of narcotic analgesics in large and increasing dosage amounts.

A disadvantage of the narcotic analgesics is the development of dependence or addiction and tolerance to 10 their action. Further, adverse reactions, including respiratory and circulatory depression, are observed when large doses are used.

Ibuprofen and flurbiprofen are non-steroidal anti-inflammato<sup>r</sup> drugs. They have been used in rheumatic and 15 degenerative diseases of the joints, for reducing platelet adhesiveness, and for dental pain.

It has now been found that, when separately or simultaneously administered to a subject, a narcotic analgesic and ibuprofen or flurbiprofen, or a salt or 20 ester thereof, can act synergically in the management of severe to moderate pain.

Narcotic analgesics are, in general, well known. Suitable such compounds for use in the present invention are the naturally-occurring opium alkaloids and their 25 semi-synthetic and synthetic derivatives. Examples are morphine, hydromorphone, oxymorphone, levorphanol, methadone, meperidine, anileridine, alphaprodine, fentanyl, codeine, codone, and oxycodone.

The narcotic analgesics are used together with 30 ibuprofen (p-isobutylhydratopic acid) or flurbiprofen (3-fluoro-4-phenylhydratropic acid) or a pharmacologically acceptable salt or ester thereof. Suitable salts are the alkali metal, alkaline earth and ammonium salts. Suitable esters are the C<sub>1-8</sub> alkyl esters, including the isomeric 35 forms thereof.

vention results in better control of pain while delaying or eliminating narcotic dependence and resistance.

5       The dosage amount initially is the usual dosage amount for the narcotic analgesic and about 50 mg of ibuprofen four or five times a day. After two days of administering the combination, the dose amount of narcotic analgesic is gradually lowered over a period of fourteen days to the lowest acceptable amount of narcotic to maintain analgesia from the combination. After fourteen days when the lowest narcotic amount is determined, the amount of ibuprofen is lowered to 100-200  
10      mg/day to maintain the same control of pain.

15      For flurbiprofen the dosage amount initially is the usual dosage amount for the narcotic analgesic and about 50 mg of flurbiprofen four or five times a day. After two days of administering the combination, the dose amount of narcotic analgesic is gradually lowered over a period of fourteen days to the lowest acceptable amount of narcotic to maintain analgesia from the combination. After fourteen days when the lowest narcotic amount is determined, the amount of flurbiprofen is lowered to 100-200 mg/day to maintain the same control of pain.

20      The narcotic analgesic and ibuprofen or flurbiprofen can be administered in the same dosage unit or can be prepared in separate dosage units and the dosage units administered at the same time. Different forms of dosage units can be used, i.e., a tablet of ibuprofen or flurbiprofen and an injection of narcotic.

25      The compositions of the present invention are preferably presented for systemic administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, suppositories, sterile parenteral solutions or suspensions, sterile non-parenteral solutions or suspensions, and oral solutions or suspensions and the like, containing suitable quantities of the synergistic combination of active ingredients.

30      For oral administration either solid or fluid unit dosage forms can be prepared.

35      Powders are prepared quite simply by comminuting the active ingredients to a suitably fine size and mixing with a similarly comminuted diluent. The diluent can be an edible carbohydrate material such as lactose or starch. Advantageously, a sweetening agent or sugar is present as well as a flavoring oil.

into formed gelatin sheaths. Advantageously, as an adjuvant to the filling operation, lubricant such as talc magnesium stearate, calcium stearate and the like is added to the powder mixture before the filling operation.

5       Soft gelatin capsules are prepared by machine encapsulation of a slurry of active ingredients with an acceptable vegetable oil, light liquid petrolatum or other inert oil or triglyceride.

10      Tablets are made by preparing a powder mixture, granulating or slugging, adding a lubricant and pressing into tablets. The powder mixture is prepared by mixing the active ingredients, suitably comminuted, with a diluent or base such as starch lactose, kaolin, di-calcium phosphate and the like. The powder mixture can be granulated by wetting with a binder such as corn syrup, gelating solution, methylcellulose solution or acacia mucilage and forcing through a screen.  
15      As an alternative to granulating, the powder mixture can be slugged, i.e., run through the tablet machine and the resulting imperfectly formed tablets broken into pieces (slugs). The slugs can be lubricated to prevent sticking to the tablet-forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The  
20      lubricated mixture is then compressed into tablets.

Advantageously, the tablet can be provided with a protective coating consisting of a sealing coat or enteric coat of shellac, a coating of sugar and methylcellulose and a polish coating of carnauba wax.

25      Fluid unit dosage forms for oral administration such as syrups, elixirs and suspensions can be prepared wherein each teaspoonful of composition contains a predetermined amount of the active ingredients for administration. The water-soluble forms can be dissolved in an aqueous vehicle together with sugar, flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydroalcoholic vehicle with suitable sweeteners together with a flavoring agent. Suspensions can be prepared of the insoluble forms with a suitable vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.  
30

35      For parenteral administration, fluid unit dosage forms are prepared utilizing the active ingredients and a sterile vehicle, water being preferred. The active ingredients, depending on the form and

hicle. In preparing solutions, the water-soluble active ingredients can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampule and sealing. Advantageously, adjuvants such as a local anesthetic, preservative and buffering agents can be dissolved in the vehicle. Cosolvents such as ethanol or propylene glycol can be used in the solvent system. Parenteral suspensions are prepared in substantially the same manner except that the active ingredients are suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The active ingredients can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active ingredients.

In addition to oral and parenteral administration, the rectal and vaginal routes can be utilized. Active ingredients can be administered by means of a suppository. A vehicle which has a melting point at about body temperature or one that is readily soluble can be utilized. For example, cocoa butter and various polyethylene glycols (carbowaxes) can serve as the vehicle.

The term "unit dosage form" as used in the specification and claims refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specification for the novel unit dosage forms of this invention are dictated by and are directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitation inherent in the art of compounding such an active material for therapeutic use in humans, as disclosed in this specification, these being features of the present invention. Examples of suitable unit dosages forms in accord with this invention are tablets, capsules, troches, suppositories, powder packets, wafers, cachets, teaspoonfuls, tablespoonfuls, dropperfuls, ampules, vials, segregated multiples of any of the foregoing and other forms as herein described.

The following examples are illustrative of the present invention, but are not intended to be limiting.

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One thousand two-piece hard gelatin capsules for oral use, each capsule containing 50 mg of ibuprofen and 15 mg morphine sulfate are prepared from the following types and amounts of ingredients:

	Ibuprofen	50 gm
5	Morphine sulfate	15 gm
	Lactose	100 gm
	Corn starch	20 gm
	Talc	20 gm
	Magnesium stearate	2 gm

10 The ibuprofen and morphine sulfate finely divided by means of an air micronizer, are added to the other finely powdered ingredients, mixed thoroughly and then encapsulated in the usual manner.

The foregoing capsules are useful for preventing pain following laparotomy by the oral administration of one capsule four times a day.

15 Using the procedure above, capsules are similarly prepared containing morphine sulfate in 7.5 and 3.75 mg amounts by substituting 7.5 and 3.75 gm of morphine sulfate for the 15 gm used above. These capsules are used to reduce the narcotic dose of the preceding examples.

20 Example 2 Soft Gelatin Capsules

One piece soft gelatin capsules for oral use, each containing 50 mg of ibuprofen and 15 mg of morphine sulfate (finely divided by means of an air micronizer) are prepared by first suspending the compounds in 0.5 ml of corn oil to render the material capsulatable and then capsulating in the above manner.

25 The foregoing capsules are useful for preventing pain following caesarian section by the oral administratin of one capsule four times a day.

Example 3 Tablets

30 One thousand tablets, each containing 50 mg of ibuprofen and 15 mg morphine sulfate are prepared from the following types and amounts of ingredients:

	Ibuprofen micronized	50 gm
	Morphine sulfate	15 gm
35	Lactose	75 gm
	Corn starch	50 gm
	Magnesium stearate	4 gm

The ibuprofen and morphine sulfate (finely divided by means of an air micronizer) are added to the other ingredients and then thoroughly mixed and slugged. The slugs are broken down by forcing them through a number sixteen screen. The resulting granules are then compressed 5 into tablets, each tablet containing 50 mg of ibuprofen and 15 mg of morphine sulfate.

The foregoing tablets are useful for preventing pain following a broken femur by the oral administration of one tablet four times a day, for two days following setting the bone.

10 Using the procedure above, tablets are similarly prepared containing morphine sulfate in 7.5 mg and 3.75 mg amounts by substituting 7.5 gm and 3.75 gm of morphine sulfate for the 15 gm used above. These tablets are used to reduce the narcotic dose of the preceding examples.

15 Example 4 Oral Suspension

One thousand ml of an aqueous suspension for oral use, containing in each teaspoonful (5 ml) dose, 100 mg of ibuprofen aluminum salt is prepared from the following types and amounts of ingredients:

	Ibuprofen, aluminum	
20	salt micronized	20 gm
	Citric acid	2 gm
	Benzoic acid	1 gm
	Sucrose	700 gm
	Tragacanth	5 gm
25	Lemon oil	2 gm
	Deionized water, q.s.	1000 ml

The citric acid, benzoic acid, sucrose, tragacanth and lemon oil are dispersed in sufficient water to make 850 ml of suspension. The ibuprofen aluminum salt (finely divided by means of an air micronizer) is stirred into the syrup until uniformly distributed. Sufficient water is added to make 1000 ml.

The composition so prepared is useful for preventing pain of cancer of the bowels at a dose of one tablespoonful (15 ml) four times a day with 1/4 gram of morphine sulfate given I.M. four times a day.

35 Example 5

A sterile aqueous solution for parenteral (i.v.) injection, containing in one liter, 350 mg of ibuprofen sodium salt is prepared

Ibuprofen sodium salt      350 mg

Water for injection, q.s. 1000 ml

To the sterile solution is added sterilized ibuprofen, sodium salt and filled into sterile containers sealed.

5        The composition so prepared is useful for preventing pain of inoperable cancer at a dose of one liter every eight hours with 1/2 grain of morphine sulfate every eight hours.

Example 6 Hard Gelatin Capsules

10      One thousand two-piece hard gelatin capsules for oral use, each capsule containing 50 mg of flurbiprofen and 15 mg morphine sulfate are prepared from the following types and amounts of ingredients:

	Flurbiprofen	50 gm
	Morphine sulfate	15 gm
	Lactose	100 gm
15	Corn starch	20 gm
	Talc	20 gm
	Magnesium stearate	2 gm

20      The flurbiprofen and morphine sulfate finely divided by means of an air micronizer, are added to the other finely powdered ingredients, mixed thoroughly and then encapsulated in the usual manner.

The foregoing capsules are useful for preventing pain following laparotomy by the oral administration of one capsule four times a day.

Using the procedure above, capsules are similarly prepared containing morphine sulfate in 7.5 and 3.75 mg amounts by substituting 25 7.5 and 3.75 gm of morphine sulfate for the 15 gm used above. These capsules are used to reduce the narcotic dose of the preceding examples.

Example 7 Soft Gelatin Capsules

30      One-piece soft gelatin capsules for oral use, each containing 50 mg of flurbiprofen and 15 mg of morphine sulfate (finely divided by means of an air micronizer) are prepared by first suspending the compounds in 0.5 ml of corn oil to render the material capsulatable and then capsulating in the above manner.

35      The foregoing capsules are useful for preventing pain following caesarian section by the oral administratin of one capsule four times a day.

15 mg morphine sulfate are prepared from the following types and amounts of ingredients:

5	Flurbiprofen micronized	50 gm
	Morphine sulfate	15 gm
	Lactose	75 gm
	Corn starch	50 gm
	Magnesium stearate	4 gm
	Light liquid petrolatum	5 gm

10 The flurbiprofen and morphine sulfate (finely divided by means of an air micronizer) are added to the other ingredients and then thoroughly mixed and slugged. The slugs are broken down by forcing then through a number sixteen screen. The resulting granules are then compressed into tablets, each tablet containing 50 mg of flurbiprofen and 15 mg of morphine sulfate.

15 The foregoing tablets are useful for preventing pain following a broken femur by the oral administration of one tablet four times a day, for two days following setting the bone.

20 Using the procedure above, tablets are similarly prepared containing morphine sulfate in 7.5 mg and 3.75 mg amounts by substituting 7.5 gm and 3.75 gm of morphine sulfate for the 15 gm used above. These tablets are used to reduce the narcotic dose of the preceding examples.

Example 9 Oral Suspension

25 One thousand ml of an aqueous suspension for oral use, containing in each teaspoonful (5 ml) dose, 100 mg of flurbiprofen aluminum salt is prepared from the following types and amounts of ingredients:

30	Flurbiprofen, aluminum salt micronized	20 gm
	Citric acid	2 gm
	Benzoic acid	1 gm
	Sucrose	700 gm
	Tragacanth	5 gm
	Lemon oil	2 gm
	Deionized water, q.s.	1000 ml

35 The citric acid, benzoic acid, sucrose, tragacanth and lemon oil are dispersed in sufficient water to make 850 ml of suspension. The flurbiprofen aluminum salt (finely divided by means of an air micronizer) is added to the

ficient water is added to make 1000 ml.

The composition so prepared is useful for preventing pain of cancer of the bowels at a dose of one tablespoonful (15 ml) four times a day with 1/4 gram of morphine sulfate given I.M. four times a day.

5      Example 10

A sterile aqueous solution for parenteral (i.v.) injection, containing in one liter, 350 mg of flurbiprofen, sodium salt is prepared from the following types and amounts of ingredients:

Flurbiprofen sodium salt    350 mg

10      Water for injection, q.s.   1000 ml

To the sterile solution is added sterilized flurbiprofen, sodium salt and filled into sterile containers sealed.

The composition so prepared is useful for preventing pain of inoperable cancer at a dose of one liter every eight hours with 1/2 grain of morphine sulfate every eight hours.

15      Example 11

Following the procedure of the proceeding Examples 1 through 10, inclusive, compositions are similarly prepared substituting equimolar amounts of the ester, e.g., methyl, ethyl, isopropyl, octyl or salts, e.g., sodium, potassium, ammonium, for the compound of the examples.

20      Example 12

Following the procedure of the preceeding Examples 1 through 10, inclusive, a dosage unit and regimen is similarly followed substituting an equi-analgesic amount each of: hydromorphone, oxymorphone, levorphanol, methadone, meperidine, alphapradine, fentanol, hydrocodone, oxycodone or codeine for the morphine of the examples.

C L A I M S

1. A process for treating pain by the systemic administration to a subject of a narcotic analgesic and ibuprofen or flurbiprofen, or a C<sub>1-8</sub> alkyl ester or a pharmacologically acceptable salt thereof.
- 5 2. A composition comprising a narcotic analgesic and ibuprofen or flurbiprofen, or a C<sub>1-8</sub> alkyl ester or a pharmacologically acceptable salt thereof.
3. A composition according to claim 2, which additionally comprises a physiologically-acceptable excipient.

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**PARTIAL EUROPEAN SEARCH REPORT**  
 which under Rule 45 of the European Patent Convention  
 shall be considered, for the purposes of subsequent  
 proceedings, as the European search report

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 Application number

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. *)
A	<b>DE - A - 1 941 583 (ELI LILLY AND COMPANY)</b> * page 11, claim 1 * & GB - A - 1 250 582 --- <b>CHEMICAL ABSTRACTS, vol. 90, no. 5, January 29, 1979</b> abstract no. 33960z, page 39 COLUMBUS, OHIO (US) & CLIN. EXP. PHARMACOL. PHYSIOL. 1978, 5(5), 503-9 D.N. SRIVASTAVA et al.: "Effect of some prostaglandin synthesis inhibitors on the antinociceptive action of morphine in albino rats" * abstract * -----	2-3	<b>A 61 K 31/485//</b> <b>(A 61 K 31/485 31/19)//</b> <b>(A 61 K 31/485 31/215)</b>
			TECHNICAL FIELDS SEARCHED (Int. Cl. *)
			<b>A 61 K</b>
<b>INCOMPLETE SEARCH</b> <p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: <b>2,3</b></p> <p>Claims searched incompletely:</p> <p>Claims not searched: <b>1</b></p> <p>Reason for the limitation of the search: Method for treatment of the human or animal body by surgery or therapy (see article 52(4) of the European Patent Convention)</p>			
Place of search <b>The Hague</b>	Date of completion of the search <b>30-09-1982</b>	Examiner <b>BRINKMANN</b>	
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technical background O : non-written disclosure		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons R : member of the same patent family corresponding	